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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,369	11/29/2000	David S.F. Young	2056.008	3138

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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	5

DATE MAILED: 02/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,369	YOUNG ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1 Claims 1-15 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities:

a. The first line of the specification should indicate that the instant application is a Divisional of 09/415,278 and not a continuation. The first line of the specification should be updated to indicate application 09/415,278 is now U.S. Patent 6,180,357.

b. Pages 26 and 30 do not contain ATCC numbers as discussed in the specification.

c. The specification contains the attorney docket number at the bottom of each page.

d. The abstract of the disclosure is objected to. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. Correction is required. See MPEP § 608.01(b).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-15 are indefinite for reciting "treating a patient suffering from a cancerous disease" because the exact meaning of the phrase is not clear. Does the phrase mean alleviating the cancer or conditions associated with cancer such as fevers, etc?

b. Claims 1-15 are indefinite for reciting "produced in accordance with a method for the production of individually customized" in claim 1 because it is not clear what "method" is being claimed or how the antibodies are "customized". In addition, it is unclear what "in accordance" means. Does the phrase mean by the same method or a method similar or a method that has a similar procedure?

c. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: What steps are needed to produce the individually customized anti-cancer antibodies and what steps determine that they are individually customized. .

d. Claim 7 is indefinite for reciting "mediated through catalyzing of the hydrolysis of cellular chemical bonds" because the exact meaning of the phrase is not clear. It is

not clear what cellular chemical bonds are being hydrolyzed or if the antibody catalyzes the reaction or if the antibody causes a cascade effect that causes the hydrolysis.

e. Claim 8 is indefinite for reciting "is mediated through producing an immune response" because the exact meaning of the phrase is not clear. Does the antibody cause an immune response or does the antibody trigger a cascade effect that causes an immune response?

f. Claim 9 is indefinite for reciting "mediated through targeting of cell membrane proteins" because the exact meaning of the phrase is not clear. Does the antibody bind to the cell membrane protein and cause cytotoxicity or does the antibody trigger a cascade effect that causes cytotoxicity that in turns interferes with the function of the protein?

g. Claim 10 is indefinite for reciting "mediated through production of a conformational change in a cellular protein" because the exact meaning of the phrase is not clear. Does the antibody causes a conformational change or does the antibody act like an enzyme and produce a reaction that causes a change in the protein such as a substrate producing a product or does the antibody cause a cascade effect that causes the conformational change?

h. Claims 13 and 15 are indefinite for reciting "ATCC Accession Number selected from the group consisting of ( )" because it is unclear what ATCC numbers are being claimed.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12-15 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of 3BD-3, 3BD-6, 3BD-8, 3BD-9, 3BD-15, 3BD-25, 3BD-26, 3BD-27, 1LN-1, 1LN-12, 1LN-14, 2LN-21, 2LN-28, 2LN-29, 2LN-31, 2LN-33, 2LN-34, and 2LN-35 and a hybridoma cell line having an ATCC number unidentified in claims 13 and 15 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species. Deposit of

the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant's referral to the deposit of the hybridomas producing the antibodies on page 26 and page 29-30 is insufficient because the specification lacks the date of deposit, as well as the ATCC numbers. In addition, if a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

7. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating colon, breast, or lung cancer in a mouse with administering antibodies wherein the antibodies are cytotoxic to cancerous cells and essentially benign to non-cancerous cells wherein the cytotoxicity is through antibody dependent cellular toxicity, complement dependent cellular toxicity, producing an immune response against a cancer antigen, targeting of proteins, wherein the method of production utilizes tissue of cancerous and non-cancerous cells, does not reasonably provide enablement for any method of treatment in a human with any antibody that is produced by any method for individual customized antibodies directed against any cancer or any fragments of antibodies that would not bind antigen or any method that is mediated by catalyzing the hydrolysis of a chemical bond or mediated

through a conformational change in a protein or a method with any antibodies recited in claims 12 and 14 which are not specific for the patient being treated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of treating a human patient, suffering from any cancerous disease by administering anticancer antibodies or fragments of antibodies which are produced by some method and which act through hydrolysis of a chemical bond which broadly reads on catalytic antibodies or a method with an antibody that mediates through a conformational change in a protein.

The specification teaches production of anti cancer antibodies that are directed against breast cancer cells and melanoma cells in vitro (see Tables 1 and 2). The specification teaches the antibodies are either cytotoxic or cytostatic (see page 8) and act through ADCC or CDC (see page 8-9). The specification fails to enable any method of treatment in a human either with patient specific antibodies or any fragments of antibodies which encompass CH1, CH2, CH3, Fc, VL or VH fragments which alone would not be cytotoxic or treatment with any anti-cancer antibodies in vivo with any cancer or antibodies produced in accordance which are individually customized for one

patient and used to treat any other patient or catalytic antibodies or antibodies that mediate through a conformational change in a protein.

The claims are not commensurate in scope with the enablement provided in the specification. The claims are broadly drawn to any antibody fragment that would not bind antigen or those that would not be cytotoxic such as those that do not comprise an Fc region. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fragments of antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function. The specification provides no direction or guidance regarding how to produce fragments of antibodies as broadly defined by the claims or

what fragments, VH, VL, CH1, CH2, CH3, Fc, etc would be cytotoxic. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claim 7 is broadly drawn to antibodies that mediate through hydrolysis of any chemical bond which is broadly drawn to catalytic antibodies, however, the specification does not enable any catalytic antibodies. The specification does not teach any transition state analogs or methods to obtain such antibodies or if such antibodies are effective as anti-cancer antibodies. The specification does not teach the antigen to which the antibodies bind and as such one skill in the art could not synthesize a transition state analog for production of a catalytic antibody or an antibody that would hydrolyze a chemical bond. As taught by Kim et al (U.S.Patent 4,963,355) catalysis using catalytic antibodies are obtained by immunization with a hapten that is related to be similar to but distinct from the selected substrate of the reaction to be catalyzed (see column 2, lines 1-11) which is a transition states analog. Thus, without knowledge of the substrate or the exact reaction to catalyze one skill in the art would not know how to produce the catalytic antibodies.

Claim 10 encompasses an antibody that produces a conformational change in a protein, however, the specification does not teach any antibody with such properties as broadly claimed. In addition, the specification does not teach how one skill in the art would produce or screen for such antibodies.

Applicant has demonstrated that the patient specific antibodies of the instant application can be used to target breast and melanoma cells in vitro. However, the claims broadly read upon the treatment of all types of cancer. As disclosed in Johnson et al (Cancer Treatment Review Vol 2 1-31 1975), Table 2, only certain types of agents

can treat certain types of cancer and that the same compound is not effective in the treatment of all types of cancers.

In addition the specification does not enable treatment in humans. Chatterjee et al state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer treatment.

The specification does not disclose whether the method is effective in patients with pre-existing tumors, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing all of the method steps, especially the treatment of tumors, is underscored by Gura et al (Science Vol 278 11/97 1041-1042) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not correlate with results expected in humans patients.

As evidenced by Seaver (1994; Genetic Engineering Vol 14(14):pages 10 and 21), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target

for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of specificity and affinity would be necessary for the antibodies of the claimed treatment method so that one skilled in the art would not be able to practice the claimed invention without undue experimentation. In addition, the specification does not teach that antibodies produced in accordance with a method for production of individually customized anti-cancer antibodies , such as those listed in claims 12-15, can be used in any patient, including those from which the tumor cells were derived from.

Therefore, in view of the broadly claimed invention, the lack of predictability in the art as evidenced by Rudikoff et al, Kim et al, Sever et al, Chatterjee et al, Gura et al, and Johnson et al, and lack of guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1-11, 13, and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Hellstrom et al (U.S. Patent 5,980,896, filed 6/14/93).

The claims recite a method for treating a patient suffering from a cancerous disease comprising administering to the patient anti-cancer antibodies produced by a

method wherein the antibodies are cytotoxic and mediated through ADCC, CDC, through hydrolysis of cellular bonds, an immune response, by targeting cell membrane proteins, by production of a conformational change in a protein, and the antibodies are cytotoxic against cancerous cells and benign to non-cancerous cells. Further claimed is a conjugate of the antibodies and a toxin, the antibodies are humanized and antibodies produced by a hybridoma.

Hellstrom et al teach antibodies for treatment of lung, colon and breast cancer in mice with antibodies produced and act through ADCC and CDC and are cytotoxic to cancerous cells and do not bind to non-cancerous cells (see Example 15 and 16). The antibodies are cytotoxic to tumor cells and benign to non-tumor cells and act through ADCC (see Example 4-6) and the antibodies were prepared by immunizing with cancer cells (see Example 1). Hellstrom also teach the antibodies can be humanized (see column 4) and the antibodies can be conjugated to a toxin (see column 3) and hybridoma cells producing the antibody (see column 15, lines 22-67). Claims 7-10 are interpreted to mean that the antibody causes the effects through a cascade effect. Since the antibodies act through ADCC and CDC it is inherent that the antibodies mediate through an immune response (Fc pathway) and since the antibodies kill the cell it would be inherent that they would mediate through targeting cell membrane proteins, produce conformational changes in proteins, and hydrolyze chemical bonds upon killing the cell.

Summary

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.
703-306-5879